Complete Summary

GUIDELINE TITLE

AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis.

BIBLIOGRAPHIC SOURCE(S)

American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. Endocr Pract 2000 Mar-Apr;6(2):162-213. [351 references]

COMPLETE SUMMARY CONTENT

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

- Dyslipidemia
- Atherosclerosis
- Coronary artery disease (CAD)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To review and sort out the current understanding of the diagnosis of dyslipidemia and provide a guideline for the treatment of lipid disorders and the relationship of these disorders to atherogenesis
- To emphasize areas recognized by clinical endocrinologists as important, such as the age of patients at screening, treatment of elderly patients, diabetes-associated dyslipidemia, role of triglycerides, and polycystic ovary syndrome
- To analyze the growing body of evidence that suggests atherogenesis is not simply a manifestation of the total cholesterol burden
- To help reverse the current patterns of under-evaluation and under-treatment of dyslipidemia

TARGET POPULATION

Screening

- All adults, 20 to 75 years old, with or without coronary artery disease (CAD) risk factors
- Adults older than 75 years old who have multiple CAD risk factors
- Children in the following groups:
    - Children older than 2 years old and adolescents with a family history of premature CAD or dyslipidemia (or both)
    - Children older than 2 years old and adolescents who smoke, have hypertension, are overweight or obese, or have diabetes
    - All adolescents older than 16 years of age

Treatment/Management

- Children older than 2 years old with dyslipidemia
- Adults with dyslipidemia. Note: special emphasis is placed on elderly patients, women, and patients with diabetes, as well as individuals with specific phenotypes [Hypercholesterolemia (Type IIa), the lipid triad (Types IIa, IIb, and IV), moderate hypertriglyceridemia (Type III), familial hypertriglyceridemia, severe hypertriglyceridemia (Type V), and isolated low high-density lipoprotein cholesterol (HDL-C)]

INTERVENTIONS AND PRACTICES CONSIDERED

Screening/Diagnosis and Risk Assessment

1. Screening all age groups, including young adults, mid-age adults, elderly and pediatric patients
    - In adults aged 20 to 75 years without coronary artery disease (CAD) risk factors: every 5 years
    - In adults aged 20 to 75 years with CAD risk factors (that is, definite myocardial infarction [MI] or sudden death before 55 years of age in

father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative): more often
    - In adults greater than 75 years old: if patient has multiple CAD risk factors, established CAD, or a history of revascularization procedures and good quality of life with no other major life-limiting disease
2. Screening tests for adults include 12-to-14 hour fasting total cholesterol, triglyceride and high-density lipoprotein cholesterol (HDL-C) profile and low-density lipoprotein cholesterol (LDL-C) levels (based on calculation or direct assay). Screening tests for children include total cholesterol, LDL-C and triglyceride levels.
3. Risk assessment including a history, physical examination, and basic lipid profile. Additional assessment includes assessment for insulin resistance, measurement of waist circumference, 12-14 hour fasting triglyceride, postprandial triglycerides, LDL subfraction B, non HDL-C evaluation, ambulatory blood pressure assessment, apo A-I evaluation, measurement of total plasma apo B, total Lp(a) level, measurement of plasma homocysteine, and consideration of factors contributing to a hypercoagulable state.

Treatment/Management

1. Smoking cessation
2. Regular physical activity
3. Nutrition therapy and weight management such as the American Heart Association - National Cholesterol Education Program (AHA-NCEP) Step I and Step II diets, low-fat diets high in soluble fiber, diets with plant stanol ester-containing margarines, moderate consumption of alcoholic beverages, and diets containing fish oils (omega-3 fatty acids).
4. Pharmacotherapy
    - Lipid-lowering drugs, including nicotinic acid (niacin), bile acid sequestrants (resins such as cholestyramine and colestipol), hydroxymethyl-glutaryl-coenzyme A reductase (statins: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin) and fibric acid derivatives (gemfibrozil and fenofibrate)
    - Monotherapy versus combination lipid-lowering drug therapy
    - Aggressive versus moderate approaches to lipid-lowering drug therapy
    - Female gender: estrogen replacement therapy
    - Diabetics: glucose-lowering agents
    - Children: lipid lowering drugs, such as the bile acid sequestrants cholestyramine and colestipol (U.S. Food and Drug Administration [FDA] approved for treating hypercholesterolemia in children), in conjunction with multivitamin supplements including folic acid and cholecalciferol.

    NOTE: Other lipid-lowering agents (statins, fibrates, and niacin) were considered for pediatric patients. Niacin is not recommended. Additional studies are needed for statins and fibrates.

5. Follow-up and monitoring, including lipid status (triglycerides, HDL-C, total cholesterol, and LDL-C levels) and side effects of therapy

MAJOR OUTCOMES CONSIDERED

- Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels
- Mortality resulting from coronary artery disease
- Risk of major coronary event
- Progression of atherosclerosis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost-to-Benefit Considerations

Although clinical trials demonstrate that aggressive lipid-lowering therapy is efficacious, the cost of this aggressive approach has been a major concern. Sufficient evidence is now available, however, to show that drug treatment of dyslipidemia is cost-effective for all men and women with established coronary artery disease (CAD) and for primary prevention when the patient has dyslipidemia and other risk factors (see Fig. 6 in original guideline document). Because of the accelerated rate of atherosclerosis in patients with type 2 diabetes mellitus, aggressive and early treatment appears to be cost-effective in these patients.

Overall Cost-Effectiveness

Usually, economic researchers evaluate CAD interventions on the basis of the cost per year of life saved, a benchmark that considers the cost difference between the new therapy and any medical treatment avoided because of the new therapy, as well as any increased survival resulting from the new therapy. Generally, any intervention that costs $40,000 to $50,000 per year of life saved is considered acceptable. This is a universally accepted benchmark for interventions such as long-term hemodialysis, breast cancer screening, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft (CABG) procedure. As shown in Figure 6 in the original guideline document, statin therapy compares very favorably with other well-accepted medical interventions for CAD and is well within the acceptable range for patients who, according to these American Association of Clinical Endocrinologists (AACE) guidelines, qualify for drug treatment. Cost-effectiveness has also been demonstrated for drugs in all other major lipid lowering drug classes. As shown in Figure 6, the cost-effectiveness of statin therapy for primary prevention is more variable than that for secondary prevention and depends on age, gender, and risk level. As would be expected, the younger the patient and the fewer the risk factors, the less cost-effective the primary prevention therapy. For example, one economic study demonstrated that the cost-effectiveness of primary prevention with lovastatin (20 mg/day) for men from 55 to 64 years old with cholesterol levels $\geq$300 mg/dL ranged from $20,200 per year of life saved for three risk factors to $78,300 per year of life saved for no risk factors (1993 dollars). In this same study, primary prevention was more expensive for women than for men but was still within the acceptable range ($40,000 per year of life saved) for women with cholesterol levels $\geq$300 mg/dL and multiple risk factors.

Clinical Application of Cost-Effectiveness Data

Although these economic data are useful for guiding treatment decisions, they should not dictate the treatment approach. Prescribing statin monotherapy and relying on an isolated cholesterol goal for all patients with dyslipidemia may ignore the heterogeneity of certain patients with CAD. To be clinically effective and therefore cost-effective, any lipid-lowering drug therapy (whether for primary

or secondary prevention) must be tailored to each patient´s dyslipidemia and risk profile.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review
Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Review was provided by the American Association of Clinical Endocrinologists (AACE) Publications Committee and three special reviewers named in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

I. Risk Factors

The lipid-associated and non-lipid-associated risk factors for coronary artery disease (CAD) are summarized as follows:

1. Lipid risk factors
   - High total cholesterol or low-density lipoprotein cholesterol (LDL-C)
   - Small, dense low-density lipoprotein (LDL)
   - Low high-density lipoprotein cholesterol (HDL-C)
   - Hypertriglyceridemia
2. Other risk factors
   - Advancing age
   - Type 2 diabetes mellitus
   - Hypertension
   - Obesity
   - Cigarette smoking
   - Family history of CAD
   - Increased levels of Lp(a) lipoprotein
   - Factors related to blood clotting, including increased levels of fibrinogen and plasminogen activator inhibitor -1 (PAI-1)
   - Hyperhomocysteinemia
   - Certain markers of inflammation, including C-reactive protein

Patients with the common lipid triad (hypertriglyceridemia, high LDL-C, and low HDL-C) have a high risk for CAD. This risk is even greater when the lipid triad is accompanied by insulin resistance, a procoagulant state, and hypertension--a condition known as the cardiovascular dysmetabolic syndrome.

Epidemiologic evidence also suggests that high HDL-C is a negative risk factor in that it confers cardioprotection in many (but not all) persons.

II. Diagnosis and Risk Assessment

Step 1: Screen

Screening for dyslipidemia is warranted for all adults up to 75 years of age regardless of CAD risk status and for adults more than 75 years old who have multiple CAD risk factors. The recommended screening schedules for dyslipidemia in various adult populations are as follows:

For young adults 20 years of age or older

- Every 5 years when no CAD risk factors are present
- More often if family history of premature CAD exists (that is, definite myocardial infarction [MI] or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)

For middle-aged adults

- Every 5 years when no CAD risk factors are present
- More often if CAD risk factors exist

For elderly patients to 75 years of age

- Every 5 years when no CAD risk factors are present
- More often if CAD risk factors exist

For elderly patients older than 75 years of age

- Evaluate if patient has multiple CAD risk factors, established CAD, or a history of revascularization procedures and good quality of life with no other major life-limiting diseases

The recommended screening tests for cholesterol and triglyceride levels are:

Evaluation	Recommended testing
Total cholesterol, triglyceride, and HDL-C profile	The 12- to 14-hour fasting profile is preferable to the nonfasting profile whenever possible The 12- to 14-hour fasting profile is essential when: • A nonfasting profile reveals total cholesterol is greater than or equal to 200mg/dL or HDL-C is less tha 35mg/dL (or both) • The patient smokes • The patient has CAD or peripheral vascular disease

	• The patient has diabetes or glucose intolerance • The patient has central obesity • The patient has hypertension • The patient has chronic renal disease • The patient has a family history of CAD
LDL-C	Calculate LDL-C by using the Friedewald equation[#]. Average two LDL-C calculations when drug therapy is being considered When fasting triglyceride levels exceed 250-300 mg/dL, use the direct LDL-C assay or non-HDL-C calculation

[#] LDL-C= (Total cholesterol -- HDL-C) -- Triglycerides / 5

Step 2: Assess Lipid-Related Risk

Serum lipid concentrations that are considered borderline or high risk include:

Lipid	Borderline serum concentration (mg/dL)	High-risk serum concentration (mg/dL)
Cholesterol	200-239	greater than or equal to 240
HDL-C	35-45	less than 35
LDL-C	130-159	greater than or equal to 160
Triglycerides[#]	150-200	great than 200

[#] Both borderline and high-risk values may signify familial combined dyslipidemia or diabetes; values >1,000 indicate high risk for pancreatitis.

When dyslipidemia exists, secondary causes must be excluded, inasmuch as treatment of an underlying contributing disease may alleviate the lipid abnormality. Once secondary causes have been ruled out, a thorough family history and physical evaluation are needed to determine the presence of additional risk factors or any genetic factors causing or contributing to the dyslipidemia. Genetic factors are particularly valuable prognostic indicators. The findings on the patient history, physical examination, and basic lipid

profile will dictate any need for additional diagnostic tests. For example, the following additional lipid tests may be useful in special circumstances:

Postprandial triglycerides

- Direct measurement may be useful when fasting triglyceride levels are marginally elevated (150 to 200 mg/dL).

LDL subfraction B

- Direct measurement of LDL subfraction B may be useful when fasting triglyceride levels are marginally elevated (150 to 200 mg/dL).

Step 3: Determine the Basic Treatment Approach

An isolated focus on LDL-C is not always sufficient to prevent heart disease in at-risk persons or to treat existing atherosclerosis. In patients with hypertriglyceridemia who have increased LDL-C or decreased HDL-C, those with triglyceride levels of 150 to 250 mg/dL can be treated with nutrition management and physical activity, whereas those with triglyceride levels that exceed 250 mg/dL should receive drug therapy; the goal should be a triglyceride level <200 mg/dL. The recommended treatment approaches for patients with dyslipidemia based on the number of CAD risk factors, the LDL-C level, and the HDL-C level are outlined as follows:

Recommended Treatment Approach Based on Coronary Artery Disease Risk and LDL-C Level[*]

Setting	Nutrition therapy, physical activity	Drug Therapy	Goal
CAD risk factors[#] less than 2	greater than or equal to 160	greater than or equal to 190	<160
CAD risk factors[#] greater than or equal to 2	greater than or equal to 130	greater than or equal to 160	<130
With atherosclerotic disease	greater than or equal to 100	greater than or equal to 130	<100
With type 2 diabetes	greater than or equal to 100	greater than or	<100

mellitus		equal to 130	

* Data are shown as mg/dL

[#] Subtract one risk factor when HDL-C $\geq$60mg/dL.

Recommended Treatment Approach for Patients With Isolated Low HDL-C

Gender	Weight loss, physical activity, smoking cessation	Drug therapy	Goal
Male	<35 mg/dL	<35 mg/dL with strong risk factors *	>35 mg/dL[#] or >45 mg/dL[$]
Female	<45 mg/dL	<45 mg/dL with strong risk factors *	>45 mg/dL[#] or >55 mg/dL[$]

* Borderline LDL-C, a family history of premature CAD, overt CAD, or any combination of these factors.

[#] In the presence of a strong family history of CAD.

[$] In the presence of overt CAD.

III. Management

The approach to prevention of atherogenesis requires management of all known risk factors. The program should include smoking cessation, regular physical activity, weight management, antiplatelet or anticoagulant therapy, management of associated metabolic conditions, and control of blood pressure in addition to treatment of the dyslipidemia.

. Physical Activity and Nutrition Therapy Dietary Recommendations from the American Heart Association and the National Cholesterol Education Program

Component	Step I diet[*]	Step II diet[#]
Total fat[$]	<30%	<30%

Saturated	<10%	<7%
Monounsaturated	5-15%	5-15%
Polyunsaturated	<10%	<10%
Carbohydrate[$]	50-70%	50-70%
Protein[$]	10-20%	10-20%
Cholesterol	<300 mg/day	<200 mg/day

A. * For healthy US population >2 yr old.
B. [#] For patients with established coronary artery disease.
C. [$] As percentage of total calories.
D. The Step I diet is recommended for the healthy US population older than the age of 2 years; the Step II diet is recommended for patients with established CAD. Patients with hypercholesterolemia should adhere to the Step II diet if the Step I diet fails to lower LDL-C values to the goal level.
E. Several other dietary approaches may also be appropriate for individual patients, including low-fat diets high in soluble fiber, diets with plant stanol ester-containing margarines, moderate consumption of alcoholic beverages, and diets containing 2 to 4 g of fish oils (omega- 3 fatty acids) per day (primarily for hypertriglyceridemia).
F. Nutrition therapy should be prescribed for at least 3 months and up to 6 months before drug therapy is initiated, unless the patient is at very high risk. In such cases, a Step II diet and lipid-lowering drug therapy are usually indicated concomitantly.

G. Lipid-Lowering Drug Therapy

When drug therapy is prescribed, the physician and patient should establish each patient's lipid goal together, and treatment should be tailored to achieve that goal. Pharmacotherapy may consist of one, two, or, in cases of extreme dyslipidemia, three agents (that is, a statin, fibrate, and niacin). The recommended pharmacologic approaches, which should be prescribed in conjunction with nutrition therapy and physical activity, are summarized as follows:

Primary lipid abnormality	Recommended approach
Hypercholesterolemia	Statin monotherapy
Hypercholesterolemia resistant to statin monotherapy	Statin + resin combination therapy. May consider adding niacin when needed to achieve lipid goal

Hypertriglyceridemia;[#] may also have low HDL-C or increased small, dense LDL (or both)	Fibrate monotherapy. Niacin monotherapy is a second choice but may be preferred for patients with concomitantly increased Lp(a)
The lipid triad[$]	Statin + fibrate combination therapy or statin + niacin combination therapy
Isolated low HDL-C	Statin monotherapy if LDL-C is borderline or increased. Niacin therapy if LDL-C is normal. Statin + niacin combination therapy if monotherapy fails to increase HDL-C to goal level

[#] Patients with familial hypertriglyceridemia do not seem to have an increased risk of CAD. Treatment should focus on reducing the risk of pancreatitis attributable to increased triglyceride level.

[$] Hypertriglyceridemia, high LDL-C, and low HDL-C.

H. Additional Treatment Considerations

1. Age. In young adult patients with dyslipidemia, lifestyle modifications (nutrition therapy, weight control, and physical activity) are essential. Drug therapy should be considered for otherwise healthy men <45 years old who have LDL-C levels >190 mg/dL that do not respond to a maximum of 6 months of conservative therapy. For other young men at risk for CAD, especially those with a family history of premature CAD, drug therapy should be considered if the LDL-C level is greater than or equal to 160 mg/dL after 6 months of conservative therapy.

   In elderly patients, as in other patient populations, global risk management is important. Drug therapy for either primary or secondary prevention is justified for high-risk patients between 65 and 75 years of age.

   Patients >75 years old who are already receiving treatment should continue any therapy that was prescribed at an earlier age. The decision to initiate therapy in this patient population should be based on the degree of risk and on individual circumstances, such as physiologic age.

2. Female Gender. In women with dyslipidemia, special consideration should be given to the following factors:

- Polycystic ovary syndrome
- Nutrition therapy
- Drug treatment
- Estrogen replacement therapy

In the presence of polycystic ovary syndrome (PCOS), a triglyceride level of >150 mg/dL and an HDL-C level <45 mg/dL may be considered specific risk factors.

In reference to nutrition therapy, research has suggested that restriction of dietary fat tends to be less effective for lowering the cholesterol level in women than in men. Dietary therapy and weight reduction, however, are effective for lowering triglyceride levels in women. For at-risk women with hypertriglyceridemia, a triglyceride level of less than or equal to 200 mg/dL should be the goal, and pharmacotherapy should be initiated if this goal is not achieved with nutrition therapy alone.

A strong rationale exists for as aggressive drug treatment of dyslipidemia in postmenopausal women as in men.

Currently, estrogen replacement therapy (ERT) may have an important role in primary CAD prevention for women who are already receiving ERT for other reasons. For most postmenopausal women with dyslipidemia, however, ERT should not be prescribed as an alternative to lipid-lowering pharmacotherapy. It may be considered lipid-lowering therapy only in lower-risk women with mildly increased LDL-C levels (130 to 160 mg/dL) and normal triglyceride levels. ERT may also allow use of a lower dosage of lipid-lowering medication. In women with hypertriglyceridemia, ERT should only be used cautiously.

IV. Dyslipidemia of Diabetes

The same risk factors that contribute to CAD in the general population contribute to CAD in patients who have diabetes, but the overall effect of each risk factor is greater.

. Identification of Risk Factors

Identifying all risk factors is important. A complete, fasting lipid panel should be measured at least yearly in adults with diabetes. Dyslipidemia in the patient with type 2 diabetes mellitus is characterized by moderate hypertriglyceridemia and low plasma HDL-C.

A. Goals of Therapy

Aggressive intervention for management of dyslipidemia is warranted for all patients with diabetes, whether or not they have established CAD. Appropriate goals for lipid levels in patients with type 2 diabetes are as follows:

	Target	Target (mg/dL)

	(mg/dL)	
Plasma lipid	Acceptable	Ideal
Triglyceride	<200	<150
Total cholesterol	<200	<170
LDL-C	<130	<100
Non-HDL-C[#]	<160	<130
HDL-C	>35	>45

[#] Total serum cholesterol minus HDL-C

B. Nonpharmacologic Intervention

Management of hyperglycemia, nutrition therapy, weight reduction in overweight patients, and increased physical activity are essential in patients with diabetes and dyslipidemia. Nutrition therapy plus physical activity alone can be pursued for 6 months in patients without established CAD in an attempt to achieve lipid goals unless the LDL-C level is increased >25 mg/dL above the goal. In such cases, pharmacotherapy can be started as early as 3 months after initiation of nutrition therapy and physical activity. In patients with established CAD, nutrition therapy, physical activity, and pharmacotherapy should be initiated concurrently.

C. Nutrition Therapy

Enlistment of the assistance of a registered dietitian is strongly recommended. In general, the patient should initially reduce total fat intake to <30% of total calories, with <10% saturated fat (AHA Step I diet). Furthermore, caloric intake should be controlled to maintain weight if the patient is lean or to reduce weight if the patient is overweight. If lipid goals are not achieved in 3 months with use of the Step I diet, the Step II diet (modified as necessary, depending on the need for weight loss) is recommended.

D. Physical Activity

Physical activity should be of moderate intensity, 30 to 45 minutes in duration, and performed 3 to 5 times a week. The pulse rate should be monitored to ensure that target levels are achieved.

E. Pharmacotherapy

Treatment with glucose-lowering agents is important and should usually be initiated before specific lipid-lowering pharmacotherapy.

When control of blood glucose is not achieved or the lipid profile fails to normalize within 4 to 6 months, treatment with appropriately selected lipid-lowering agents is warranted. Of importance, waiting any longer is inappropriate. A borderline or normal LDL-C level should not obscure the need for pharmacotherapy, in light of the propensity for these patients to carry the small, dense LDL pattern. The choice of therapy should be based on the nature of the dyslipidemia and the special needs of the patient with diabetes.

Recommended Pharmacologic Therapy for Patients with Type 2 Diabetes Mellitus and Dyslipidemia

Primary lipid abnormality	Recommended approach
Hypercholesterolemia	Statin monotherapy. Consider a resin or a low-dose statin + resin combination for refractory patients with substantially increased LDL-C without concomitant hypertriglyceridemia
Hypertriglyceridemia with or without low HDL-C	Fibrate monotherapy
Combination of hypercholesterolemia and hypertriglyceridemia	Aggressive glycemic control and high-dose statin or fibrate therapy. Consider combination statin + fibrate or statin + low-dose niacin therapy for selected patients when monotherapy fails to achieve lipid goal

V. Dyslipidemia in Pediatric Patients

The AHA Step I diet is recommended for all healthy children >2 years old.

. Screening

A total cholesterol, LDL-C, and triglyceride profile should be determined for all the following:

- Children >2 years old and adolescents with a family history of premature CAD or dyslipidemia (or both)
- Children >2 years old and adolescents who smoke, have hypertension, are overweight or obese, or have diabetes
- All adolescents >16 years of age

When the lipid profile is interpreted in children and adolescents, the clinician should be aware that lipid levels fluctuate during childhood and adolescence. In addition, a low HDL-C level may not have the same implications in children as it does in adults. Some investigators have found that girls tend to have higher plasma cholesterol levels than do boys throughout childhood and adolescence.

The lipid screen should be repeated when the LDL-C level exceeds 110 mg/dL. Nutrition therapy, regular physical activity, and risk factor management are warranted for a verified LDL-C level of 110 to 129 mg/dL; more intensive dietary therapy and pharmacotherapy may also be warranted in some pediatric patients with LDL-C levels greater than or equal to 130 mg/dL.

A. Intervention

Dyslipidemia in pediatric patients necessitates global risk factor management and lifestyle counseling. This holistic approach is essential for children and adolescents.

0. Nutrition Therapy

Low-fat diets can reduce the total cholesterol level and have a significant but modest effect on the LDL-C level in pediatric populations. When a low-fat diet is prescribed for children or adolescents, the following information must be considered:

- Total cholesterol and HDL-C levels are positively correlated until the age of 20 years, and lower-fat diets that reduce total cholesterol have been associated with HDL-C reductions.
- Increased intake of carbohydrates may increase plasma triglyceride concentrations in children.
- Fish oil supplements have a profound effect on serum triglyceride levels in children and have been used in pediatric patients with end-stage renal insufficiency.
- Water-soluble fiber does not reduce the serum cholesterol level in children as it does in adults.

Use of the AHA Step II diet may be attempted when a child or adolescent fails to respond to the Step I diet. Close monitoring of all lipid levels is imperative to ensure adequate intake of nutrients and energy.

1. Drug Therapy

Because the potential long-term effects of lipid-lowering drug therapy on growth, development, and biochemical variables are unclear, the prescribing decisions must be based on empiric and indirect evidence and the needs of the patient. When the

need for lipid-lowering drug therapy is assessed in pediatric patients, the following factors must be considered:

- The effectiveness of delaying treatment until adulthood
- The nature of the pediatric dyslipidemia

Children and adolescents with genetic dyslipidemias should be treated with lipid-lowering drugs, when needed, to achieve LDL-C levels <130 mg/dL. A persistent increase in LDL-C coupled with parental history of dyslipidemia may predict the presence of an underlying genetic disorder.

Cholestyramine and colestipol are the only approved drugs for treating hypercholesterolemia in children. They are not associated with systemic toxicity or other serious adverse or toxic effects. LDL-C reductions of 15 to 20% are possible with relatively low dosages of cholestyramine (8 g/day) or colestipol (10 g/day). These agents should not be used in children with hypertriglyceridemia. They should be prescribed in conjunction with multivitamin supplements, including folic acid and cholecalciferol.

Long-term studies are needed to assess the potential effects of statins in children. Investigators have suggested that small doses of statins may be useful for boys with severely increased cholesterol levels who are approaching the end of the maturation process, as a supplement to dietary and resin therapy.

Additional study is also needed before fibrates can be recommended. Niacin is not recommended for this population.

VI. Follow-Up and Monitoring

For all patients receiving intervention of any type, the lipid status should be assessed 4 to 6 weeks after therapy is instituted and again at 6-week intervals until the treatment goal is reached. At each 6-week interval, the physician should monitor the response to and side effects of therapy. Thereafter, once the lipid goal has been achieved, consultations should be scheduled at 6- to 12- month intervals. The precise interval depends on patient adherence to therapy and the consistency of the lipid profile. In addition, certain clinical circumstances warrant more frequent evaluation. The lipid status should always be reassessed in the following situations:

- Control of diabetes has deteriorated over time
- The patient has been prescribed a new drug known to affect lipid levels
- The patient's cardiovascular status has changed
- The patient has gained considerable weight
- A recent lipid profile has revealed an unexpected adverse change in any lipid level
- A new risk factor has been identified

Both triglyceride and HDL-C concentrations should be part of each follow-up lipid assessment, along with serum total cholesterol and LDL-C levels. These factors are especially important in patients with type 2 diabetes mellitus and in those with macrovascular disease. Some patients who have had their LDL phenotype determined may need reanalysis of the phenotype, particularly if their clinical status deteriorates or if lipid-lowering drug therapy has been altered. This reanalysis should be performed only after the patient has received lipid-lowering drug therapy for greater than or equal to 3 months.

Consultation with an endocrinologist or lipid specialist is recommended when uncontrolled diabetes and dyslipidemia coexist, when unusual or refractory lipid levels persist despite treatment, or when CAD manifests despite favorable lipid levels.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation. However, the recommendations are based on a comprehensive review of numerous trials. Specifically, the clinical efficacy of lipid-lowering pharmacologic agents was based on recent, large-scale controlled trials. Study designs are discussed in detail in the guideline document. In those instances where clinical evidence is limited, this is noted in the text of the guideline.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and effective treatment and management of dyslipidemia may:

- Reduce mortality associated with coronary artery disease (CAD)
- Prevent and/or stabilize existing CAD.
- Reduce low-density lipoprotein cholesterol (LDL-C) and increase high-density lipoprotein (HDL-C) and thereby reduce the risk of a primary and secondary major coronary events in both men and women.
- Reduce the incidence of ischemic events.

Compelling and abundant scientific, epidemiologic, and clinical evidence shows that treatment of dyslipidemia (through nutrition therapy and physical activity, with or without drug therapy) not only lowers the risk of primary and secondary coronary events but also can slow, prevent, or even reverse the progression of atherosclerosis.

Diagnosis and Risk Assessment

- Identification of risk factors enables the physician to tailor the therapy for dyslipidemia to each patient's risk level and thereby maximize treatment effectiveness.

Management

Physical Activity and Nutrition (Diet) Therapy

- Nutrition therapy can help control other coronary risk factors
- Nutrition therapy plus physical activity or smoking cessation can slow the progression of CAD.
- Hypertriglyceridemia can be highly responsive to nutrition therapy.
- Nutrition therapy has diagnostic significance. Patients who do not respond to nutrition therapy despite good adherence are more likely to have genetic dyslipidemia
- Diets that are both high in fiber and low in fat can yield cholesterol reductions of 10 to 15%, and studies of fiber supplements added to the Step I diet show an additional 9% decrease in LDL-C levels over the Step I diet alone.
- Substitution of conventional home dietary fats with a margarine containing plant stanol esters can reduce LDL-C levels by approximately 10 to 20%.
- Ingestion of 2 to 4 grams of fish oils per day can decrease triglyceride levels by 25% or more while slightly increasing LDL-C levels (4% versus placebo) and producing no significant effect on HDL-C. In addition, fish oils - either ingested through a high-fiber diet containing approximately 600 mg of oily fish per day or given as daily supplementation of 2 g of the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid - can lower cardiac events and associated mortality in men with coronary artery disease after 1 to 2 years.

Pediatric patients.

Clinical studies have shown that low-fat diets can reduce total cholesterol level and have a significant but modest effect on LDL-C level in pediatric populations.

Pharmacotherapy

- Clinical evidence suggests that lipid-lowering drug therapy can both prevent CAD from developing and stabilize early, occult lesion. In addition, occlusive lesions can be clinically reversed after aggressive treatment with lipid-lowering drugs.
- Some investigators have reported that aggressive LDL-C lowering as low as < 85 mg/dL may benefit many patients--including certain patients with average or elevated LDL-C levels, those who have the small, dense LDL pattern B, and patients who have undergone a coronary artery bypass (CABG) procedure.

Lipid-lowering drugs. [Current lipid-lowering drugs include nicotinic acid (niacin), bile acid sequestrants (resins), hydroxymethyl-glutaryl-coenzyme A reductase inhibitors (statins), and fibric acid derivatives (fibrates)]

Although the clinical efficacy trials were not designed to demonstrate an overall reduction in mortality, some follow-up research has revealed a long-term overall decrease in mortality.

Statin monotherapy.

- Major coronary prevention trials clearly show that statin monotherapy is beneficial for both primary and secondary prevention of acute coronary events in at-risk patients with increased cholesterol or average (<264 mg/dL with LDL-C <190 mg/dL) cholesterol levels.

Fibrate monotherapy.

- Both gemfibrozil and fenofibrate are effective for treating patients with severe hypertriglyceridemia and for patients at risk for CAD who have an increased triglyceride level or low HDL-C level (or both) as the primary lipid abnormality.

Niacin monotherapy.

- Niacin is a powerful LDL-C- and triglyceride-lowering drug that also substantially increases HDL-C. Niacin produces a more favorable lipid response than a fibrate, has been associated with angiographic evidence of regression of CAD, and has been associated with reduced mortality 9 years after discontinuation of use. Generally, however, niacin is considered second choice after fibrates for lowering triglyceride levels and raising HDL-C levels because of its side effect profile (See Potential Harms).

Combination therapy.

- For patients with severely elevated cholesterol levels in whom monotherapy does not achieve the therapeutic goal, adding a drug with a complementary mode of action may be more cost-effective than increasing the statin dosage.
- Lower dosages of two or more drugs may avoid or minimize toxicity associated with higher dosages of a single drug.
- For patients with increased cholesterol and triglyceride levels, a combination regimen may be warranted to lower both cholesterol and triglyceride levels and to raise the HDL-C level.

Female gender.

- A strong rationale exists for treating dyslipidemia as aggressively in postmenopausal women as in men. Lipid-lowering drug therapy can benefit women as much as it benefits men.
- Estrogen replacement therapy (ERT), with or without progestin, has been shown to reduce LDL-C levels by 10 to 24% in postmenopausal women. ERT may have an important role in primary CAD prevention in women who are already receiving ERT for other reasons (such as menopausal symptoms or prevention of osteoporosis). In epidemiologic studies, ERT is almost universally linked with reduction of CAD risk.

Diabetic patients.

- Nutrition therapy, weight loss, and daily physical activity for 30 minutes or more will often decrease insulin resistance, decrease plasma triglyceride and VLDL levels, increase HDL-C, and lower LDL-C 15 to 25 mg/dL.
- Triglyceride levels usually decline with better glucose control, and optimal glycemic control may decrease LDL-C levels by 10 to 15%.
- For the patient with hypercholesterolemia as the primary lipid disorder, statins are recommended. Statins are generally well tolerated, do not effect glycemic control, and have been shown to have equivalent lipid-lowering properties in patients with and those without diabetes.
- Fibrates are the agents of choice for treating primary or isolated hypertriglyceridemia when efforts to control plasma glucose fail to lower triglyceride levels. Both gemfibrozil and fenofibrate can decrease plasma triglyceride levels and increase HDL-C levels in patients with type 2 diabetes without affecting glycemic control; fenofibrate can also reduce total cholesterol and LDL-C levels in these patients.

Pediatric patients.

- Bile Acid Sequestrants. Cholestyramine and colestipol are the only approved drugs for treating hypercholesterolemia in children. Pediatric studies have generally demonstrated LDL-C reductions of 15 to 20% with bile acid sequestrant therapy, and recent evidence shows that these reductions are possible with relatively low dosages of cholestyramine (8 g/day) or colestipol (10 g/day).

POTENTIAL HARMS

Nutrition therapy. The only known side effect of supplementation with a concentrated omega-3-fatty acid product is eructation.

Pharmacotherapy. The most frequent, main drawbacks of the primary lipid lowering drug classes are:

Niacin (nicotinic acid).

- Deleterious effect on serum glucose at higher doses
- Increases uric acid levels
- Potential for hyperuricemia, hepatotoxicity (rare but may be severe), peptic ulcer, frequent skin flushing, pruritus, nausea, abdominal discomfort
- Only 50-60% of patients can tolerate nicotinic acid in effective doses for a prolonged time

Bile acid sequestrants (cholestyramine, colestipol).

- May increase serum triglycerides
- Frequent non-life-threatening gastrointestinal (GI) events, which can reduce patient adherence
- Many potential drug interactions

- May reduce absorption of folic acid and fat-soluble vitamins such as vitamins K, A, and D

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin).

- Monitoring of liver function required
- Muscle aches and fatigue in a small proportion of patients

Fibric acid derivatives (gemfibrozil, fenofibrate)

- Gemfibrozil may increase LDL-C 10-15%
- GI symptoms, possible cholelithiasis, myopathy when used with other agents
- May potentiate effects of orally administered anticoagulants
- Gemfibrozil may increase fibrinogen level
- Gemfibrozil and fenofibrate can increase homocysteine independent of vitamin concentrations
- Rhabdomyolysis when used with statin (rare)

Additional pharmacotherapy considerations include:

- Some research has shown that pravastatin and fluvastatin are both relatively safe for patients needing cyclosporine, but lovastatin therapy has been shown to result in rhabdomyolysis.
- For patients receiving statin-fibrate combination therapy, careful monitoring for liver toxicity is essential for all patients, and patients should be informed to alert their physician if they experience "flu-like" symptoms of myalgias and malaise or severe muscle pain.
- Statin-niacin combination therapy is often avoided because of the risk of muscle and liver toxicity. One study designed to assess the safety and effectiveness of this therapeutic combination showed a 53% mean increase in alanine aminotransferase and a 42% mean increase in aspartate aminotransferase related to the use of sustained-release niacin at a target dosage of 1 g twice a day.
- Niacin monotherapy may increase mean plasma glucose levels and glycosylated hemoglobin in patients with type 2 diabetes mellitus.
- Combination of statin and fibrate increases the risk of myopathy in patients with diabetes. The presence of renal disease may considerably increase the risk of myopathy and should be avoided in patients with increased creatinine levels.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. Endocr Pract 2000 Mar-Apr;6(2):162-213. [351 references]

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GUIDELINE DEVELOPER(S)

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GUIDELINE COMMITTEE

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An update is not in progress at this time.

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Print copies: Available from AACE, 1000 Riverside Ave., Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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